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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/872,063	06/01/2001	Yuk-Ming Dennis Lo	JAK-PT001.1	3772

3624 7590 02/25/2004

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EXAMINER	
GOLDBERG, JEANINE ANNE	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 02/25/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/872,063	LO ET AL.	
	Examiner	Art Unit	
	Jeanine A Goldberg	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 December 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *37-48* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *37-48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the papers filed December 16, 2003. Currently, claims 37-48 are pending.

2. All arguments have been thoroughly reviewed but are deemed non-persuasive for the reasons which follow.

New Matter

3. Claims 37-48 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In the amended claims, references to "nucleic acid of interest, associated with a genetic trait, condition or abnormality **not present** in the pregnant female" are included. The does not indicate where in the specification support may be found. However, the specification does not describe or discuses "nucleic acid of interest, associated with a genetic trait, condition or abnormality **not present** in the pregnant female." The response filed May 13, 2002, on page 7, indicates the continuing application is seeking to obtain claims which more fully reflect the generality of the invention. The response has broadened the claims from paternally inherited, which was patented, to detecting the presence of a fetal nucleic acid which differs from that of the maternal genome, because the term "paternally inherited" dies not cover the cases where (a) the gene is maternally inherited, yet is not the same as the fetus as in the mother and (b) the gene

is altered spontaneously. The specification does not encompass these two situations in which applicant is seeking to protect. Instead the specification describes "determination of any maternal or fetal condition or characteristic which is related to either the fetal DNA itself or to the quantity or quality of the fetal DNA in the maternal serum or plasma" (page 3 of specification). The specification further describes the method can be applied to the detection of any paternally-inherited sequences which are not possessed by the mother and which may be for example gene which confer a disease phenotype in the fetus (page 4). This description does not support detecting the presence of a fetal nucleic acid which differs from that of the maternal genome. While the concept of detecting fetal nucleic acids which are paternally inherited in maternal serum/plasma, the specification does not support the concepts of either nucleic acids which differ between maternal genome and fetal genome and spontaneous differences. The concept of "nucleic acid of interest, associated with a genetic trait, condition or abnormality **not present** in the pregnant female" does not appear to be completely supported as part of the originally filed invention. The specification does not appear to have contemplated either spontaneous alterations in the egg and sperm nor differences between maternal and fetal nucleic acids which are argued to be encompassed by the instant claims. Therefore, "nucleic acid of interest, associated with a genetic trait, condition or abnormality **not present** in the pregnant female" constitutes new matter. The response has not argued or specifically pointed out support for this new subject matter or the subject matter intended to be encompassed by the claims as stated in the May 13, 2002 response.

Claims 38, 40-41, 45 discuss a comparison between the maternal genome of the pregnant female by comparison to the maternal free of contamination by fetal nucleic acids. The claim appears to extend beyond the scope of the originally filed disclosure. The specification does not appear to support any particular comparison between maternal genome while carrying the fetus and free of contamination by fetal nucleic acids. The specification does not appear to have contemplated such a comparison. Applicant is requested to point out support in the originally filed specification.

Claim 46 is drawn to a method employing two probes, one to an aneuploidal trait, condition or abnormality and the second to a chromosome not responsible for an aneuploidal trait, condition, or abnormality. The specification does not appear to contemplate an assay requiring two probes, one to an aneuploidal sequence and one to a non-aneuploidal sequence. The subject matter does not appear to be supported by the instant specification.

Applicant is required to cancel the new matter in the reply to this Office Action.

Response to Arguments

The response traverses the rejection. The response asserts that the specification does provide support for the concept. The response points to paragraph 9 of the patent publication to extend the invention to fetal abnormalities such as chromosomal aneuploidies or simple mutations. The response also argues that the broad definition is not limited to paternally-derived traits, or traits in both the fetus and the pregnant woman. The response continues to argues that "it is more likely than not that the pregnant female would not have the same abnormality as the fetus." And the

response concludes that the specification contemplates that a nucleic acid of interest, associated with a genetic trait, condition or abnormality not present in the pregnant female. This argument has been reviewed but is not convincing because the broad disclosure in the specification does not specifically contemplate a genetic trait, condition or abnormality not present in the pregnant female. With regard to the argument that "it is more likely than not that the pregnant female would not have the same abnormality as the fetus," this appears to be attorney arguments. MPEP 716.01(c) makes clear that "The arguments of counsel cannot take the place of evidence in the record. In re Schulze , 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965). The statement is made without any evidence and the examiner does not see any support in the specification for such an assertion. Based upon the amendment filed May 13, 2002, it is clear that applicant's wish for their new amendments to encompass cases (a) in which a gene is maternally inherited, yet the nucleic acid is not (in total) the same in the fetus as in the mother, and (b) in which the gene is altered spontaneously, for example, in the egg or sperm, i.e. by what appears to be chance or sporadic mutation. The response has provided no support for each of these embodiments within the broad class of claimed nucleic acids.

The response points to Example 2 to try to obtain broad scope based upon a single embodiment. The illustration of a single aneuploidal abnormality of SRY DNA does not provide written description for all maternally inherited nucleic acids which are not the same in the fetus as in the mother.

The response argues that the specification is not limited to paternally-derived fetal traits. The specification does not appear to contemplate the broad scope of the claims directed to nucleic acid of interest, associated with a genetic trait, condition or abnormality not present in the pregnant female. While the specification may not limit the invention to paternally inherited, the specification does not support the broad scope of nucleic acid of interest, associated with a genetic trait, condition or abnormality not present in the pregnant female. The disclosure of paternally inherited nucleic acids in the instant specification does not mean that the specification also supports maternally inherited.

The response also traverses the rejection as applied to Claims 38, 40, 41, and 45. The response asserts that a comparison was performed between maternal genome while carrying the fetus and free of contamination by fetal nucleic acid (response page 13). This argument has been thoroughly reviewed, but is not found persuasive because the example provided does not particularly indicate that the sample is free from contamination of fetal nucleic acids.

With respect to the example 5, the females who were studied prior to conception were not pregnant females, as required by the claims. Thus, this example is not commensurate in scope with the claims and is not considered relevant to the claimed invention.

With regard to Claim 46, the response directs the examiner's attention to paragraph 20 of the patent application publication. This argument has been thoroughly reviewed, but is not found persuasive because the cite provided by applicants is not

directed to probe detection. In fact the paragraph is directed to PCR techniques. PCR techniques do not require probes. Thus, the argument is not found persuasive.

Thus for the reasons above and those already of record, the rejection is maintained.

Priority

4. This application is a continuation of 09/380,696, filed November 29, 1999, now patent US Pat. 6,258,540 and a 371 of GB98/00690, filed March 4, 1998. This application also claims priority to GB9704444, filed March 4, 1997.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 37-48 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for detecting a paternally inherited nucleic acid of fetal origin performed on a maternal serum or plasma sample from a pregnant female, which comprises amplifying a paternally inherited nucleic acid from the serum or plasma sample and detecting the presence of a paternally inherited nucleic acid of fetal origin in the sample, does not reasonably provide enablement for a detection method performed on serum or plasma for a nucleic acid of interest, associated with a genetic trait, condition or abnormality no present in the pregnant female by amplifying and identifying the presence in the sample of the nucleic acid of

fetal origin. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to us the invention commensurate in scope with these claims.

The claims are broadly drawn to a detection method performed on serum or plasma of a pregnant woman to detect a nucleic acid of interest, associated with a genetic trait, condition or abnormality no present in the pregnant female by amplifying and identifying the presence in the sample of the nucleic acid of fetal origin.

The specification teaches fetal DNA has been detected in both serum and plasma. Table 2 and 3 show the quantification of fetal DNA in maternal serum and plasma in relation to the gestational age (pg. 33). The specifications teaches the detection of the Y-chromosome by markers to DYS14 locus and SRY gene. The specification teaches that plasma and serum samples were collected from 43 pregnant women with gestational ages from 12 to 40 weeks (pg. 9, para. 1). Of the 30 male fetuses, detection of a Y-positive signal occurred in 24 plasma samples and only 21 serum samples (pg. 9,para. 1). The specification also teaches a RhD status determination from plasma of RhD-negative pregnant women (pg. 15 and Table 1, pg. 20). The specification teaches that the DNA detected is paternally inherited (page 4, para 18) and requires amplification.

The art teaches the detection of fetal DNA in maternal plasma for an expanded CGT trinucleotide repeats, in the DM kinase gene on chromosome 19, in the range of 50-4000 repeats (Amicucci et al, February 2000, Clinical Chemistry, Vol. 46, No. 2, pages 301-302). Amicucci teaches sampling of plasma from pregnant women at 10

weeks of gestation to detect the expanded repeat present only in the father. Amicucci states "at present, this test seems appropriate only for monitoring paternally inherited expanded alleles" (pg. 302, para. 2). Additionally, Lo (Annals of Medicine, Vol. 31, NO. 5, pg. 308-312, Oct 1999) states "the success of the detection of fetal-derived RhD gene in the plasma and serum of pregnant women opens up the possibility that a similar approach may be used for other single-gene disorders" (pg. 310, col. 2, para. 3). However, Lo has not taught single gene disorders other than RhD which may in fact use this technique. Furthermore, the RhD analysis was only shown to be successful on RhD-negative women. The language of the paper is that of suggestion, and hypothesis rather than of evidence that this method works for these suggested single-gene disorders.

The art provides a summary of the state of the art (Pertl et al. Obstet Gynecol, Vol. 98, No. 3, pages 483-90, September 2001). Pertl et al (herein referred to as Pertl) teaches that a search was conducted of the art from 1970-2000 and provides a summary of the state of the art. Pertl teaches that the "diagnostic use of circulating fetal DNA in maternal plasma is currently limited to genes that are present in the fetus but not in the mother". Pertl suggests that "the main limitation at present appears to be the availability of uniquely fetal gene sequences that will identify the presence of fetal DNA in both male and female fetuses" (page 484). Pertl also discusses the detection of fetal aneupoidy, such that "this method can be applied only to a very small number of paternally inherited fetal aneuploidies. Furthermore, the selected markers must be

informative, with both paternal alleles sizes differing from those of the mother." (page 487, col. 2).

The detection of a nucleic acid of interest, associated with a genetic trait, condition or abnormality not present in the pregnant female by amplifying and identifying the presence in the sample of the nucleic acid of fetal origin. A pregnant female may be a carrier for a nucleic acid associated with a genetic trait. The pregnant female may not have to condition, abnormality or genetic trait. For example, a pregnant female may be a carrier for a particular mutation in the gene, but the absence of two copies of the mutation does not yield a genetic trait, condition or abnormality (i.e. diabetes, hair color, schizophrenia). Therefore, the detection of the nucleic acid associated with the genetic trait, condition or abnormality (i.e. diabetes, hair color or schizophrenia) in maternal serum does not indicate that the nucleic acid is of fetal origin. Detection of a nucleic acid of interest, associated with a genetic trait, condition or abnormality no present in the pregnant female by amplifying and identifying the presence in the sample of the nucleic acid of fetal origin is unpredictable since there are numerous instances where females may be carriers, but fail to exhibit a genetic trait, condition or abnormality. In order to conclude that the detected nucleic acid is of fetal origin, the nucleic acid could not also be present in the maternal genome. For the reasons above, in the new matter rejection, the instant specification does not appear to be directed to spontaneous mutations or to differences between maternal and fetal DNA. The specification explicitly states that "the method of the invention can be applied to the detection of any paternally-inherited sequences which are not possessed by the mother" (pg. 4, lines 5-

7). As stated in numerous of the papers the concentrations of fetal DNA in maternal plasma may reach 3.4% in early pregnancy and 6.2% in late pregnancy, however, there is a much higher percentage of maternal DNA in the plasma. Provided that the skilled artisan obtained a positive result for detection of the nucleic acid, it would require undue experimentation determine whether the nucleic acid was a results of the maternal DNA found in the maternal plasma or whether in fact the nucleic acid was from the fetus.

It is not unpredictable to detect a mutation in a nucleic acid which is found in the maternal genome. However, it is unpredictable whether the nucleic acid on which the mutation or alteration was found is a fetal nucleic acid. The maternal serum/plasma contains not only fetal DNA but also maternal DNA. Therefore, detection of a nucleic acid in the maternal serum/plasma does not indicate that the nucleic acid found is fetal DNA. The specification does not provide any teachings nucleic acids which are specific to the fetus and absent in the maternal serum/plasma. Thus, detection of a nucleic acid of interest, associated with a genetic trait, condition or abnormality no present in the pregnant female by amplifying and identifying the presence in the sample of the nucleic acid of fetal origin would be unpredictable and require undue experimentation.

Thus, the above analysis demonstrates that the skilled artisan would be required to perform undue experimentation to make and use the invention as claimed.

Response to Arguments

The response traverses the rejection. The response asserts that the instant claims do not encompass the situation where the female possesses only one copy of the mutation in her genome such that she will not demonstrate the phenotypic

expression. This argument has been thoroughly reviewed, but is not found persuasive because the claims are directed to identifying a nucleic acid of interest associated with a genetic trait, condition or abnormality not present in the pregnant female. The claim is broad enough to encompass such a recessive gene which is associated with a trait, condition or abnormality. The abnormality, trait and condition are not present in the pregnant female, but the nucleic acid may be present. Applicant's may be arguing a slightly different interpretation such that the nucleic acid of interest is not present in the pregnant female rather than the genetic trait, condition or abnormality is not present in the pregnant female. The claim, however, as written, appears to have the "not" following the genetic trait, condition or abnormality, rather than the nucleic acid. It is noted that clarification, would not appear to overcome the new matter rejection.

The response argues that the specification does not limit the invention to paternally-derived fetal traits. This argument has been reviewed and thoroughly addressed above in the New Matter rejection.

The response appears to assert that the post filing date references are not pertinent to the issue of enablement. This argument has been thoroughly reviewed, but is not found persusasive because in the event that the post filing date art is unable to accomplish the method as recited, without more, it is unpredictable that at the time of filing the method could be enabled.

First, Amicucci states "at present, this test seems appropriate only for monitoring paternally inherited expanded alleles" (pg. 302, para. 2). This statement was made in 2002 which is approximately four years after the earliest filing date of the instant

application. Given the state of the art four years after the filing date, the art teaches that "this test seems appropriate only for monitoring paternally inherited expanded alleles."

Second, Lo, in 1999 after the filing of the application, states "the success of the detection of fetal-derived RhD gene in the plasma and serum of pregnant women opens up the possibility that a similar approach may be used for other single-gene disorders" (pg. 310, col. 2, para. 3). However, Lo has not taught single gene disorders other than RhD which may in fact use this technique. Furthermore, the RhD analysis was only shown to be successful on RhD-negative women. It is clear that one of the inventors of the instant application did not recognize or appreciate that the invention could be used for additional applications. At the time the invention was made, the applicant must be in possession of the claimed invention. Based upon the statements in the paper, it does not appear that applicants were in possession of the application.

Finally, in 2001 Pertl states after reviewing the art that the "diagnostic use of circulating fetal DNA in maternal plasma is currently limited to genes that are present in the fetus but not in the mother". Pertl, a skilled artisan, suggests that "the main limitation at present appears to be the availability of uniquely fetal gene sequences that will identify the presence of fetal DNA in both male and female fetuses" (page 484). Pertl also discusses the detection of fetal aneupoidy, such that "this method can be applied only to a very small number of paternally inherited fetal aneuploidies. Furthermore, the selected markers must be informative, with both paternal alleles sizes differing from those of the mother." (page 487, col. 2).

Although applicant argues that none of these references add any information to the issue of enablement, this argument does not appear to be supported. The record provides evidence to suggest that at the time the invention was made, i.e. the time of filing the claimed invention was not enabled. This argument has been reviewed but is not convincing because the

Thus for the reasons above and those already of record, the rejection is maintained.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

6. Claims 37-48 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-27 of U.S. Patent No. 6,258,540, July 10, 2001. Although the conflicting claims are not identical, they are not patentably distinct from each other. The claims of the instant application are drawn to methods performed on serum or plasma for a nucleic acid of interest, associated with a genetic trait, condition or abnormality no present in the pregnant female by amplifying and identifying the presence in the sample of the nucleic acid of fetal origin. The claims

of patent 6,258,540 are drawn to methods of detecting paternally inherited DNA of fetal origin by amplifying the paternally inherited nucleic acid from plasma or serum and detecting the presence of the fetal DNA.

Response to Arguments

The instant response filed December 16, 2003 traverses the rejection. The response asserts that the office action fails to analyze the claims of the patent and the instant claims. Moreover, the response asserts that domination "by itself cannot support a double patenting rejection." This argument has been thoroughly reviewed, but is not found persuasive because an obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claim(s) because the examined claim is either anticipated by or would have been obvious over, the reference claim(s). See e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985).

Although the conflicting claims are not identical, they are not patentable distinct from each other because the claims of the instant application is generic to all that is recited in Claim 1-27 of U.S. Patent No. 6,258,540. That is, Claims 1-27 of 6,258,540 falls entirely within the scope of the instant claims or in other words, the claims of the instant application are anticipated by Claims 1-27 of 6,258,540.

The response asserted in the response filed May 13, 2003 and December 16, 2003 that applicants intend to submit a terminal disclaimer when the other issues of

Patentability are resolved. Thus for the reasons above and those already of record, the rejection is maintained.

Conclusion

7. **No Claims allowable.**
8. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (571) 272-0743. The examiner can normally be reached Monday-Friday from 6:00 a.m. to 3:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (571) 272-0745.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (571)272-0507

J. Goldberg

Jeanine Goldberg
Patent Examiner
February 23, 2004

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2/23/04